cit

L33 ANSWER 19 OF 40 MEDLINE
AN 95034751 MEDLINE
TI Exploring the microtubule-binding region of bovine ***microtubule*** - ***associated*** ***protein*** -2 (MAP-2): ***cDNA*** sequencing, bacterial ***expression*** , and site-directed mutagenesis.
AU Coffey R L; Joly J C; Cain B D; Purich D L
CS Department of Biochemistry and Molecular Biology, University of Florida College of Medicine, Gainesville 32610-0245..
NC GM-44823 (NIGMS)
SO BIOCHEMISTRY, (1994 Nov 15) 33 (45) 13199-207.
Journal code: A0G. ISSN: 0006-2960.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
OS GENBANK-S74025
EM 9502
AB A 1.1 kilobase fragment of bovine ***microtubule*** - ***associated*** ***protein*** -2 (MAP-2) ***cDNA*** coding for bovine MAP-2 microtubule-binding region (MTBR) was sequenced. Relative to mouse, rat, and human MAP-2, we observed striking preservation of primary structure, even beyond the sequence and spacing of the three nonidentical peptide repeats responsible for microtubule-binding interactions. For further analysis of microtubule-MAP interactions using site-directed mutagenesis, we developed a bacterial ***expression*** system coding for the MT-binding fragment of MAP-2 starting at the thrombin cleavage site (position 1629) and continuing to the C-terminus. This MT-binding fragment was ***purified*** to homogeneity by taking advantage of the unusual heat-stability and isoelectric properties of this cytomatrix component. We found that the MT-binding domain readily promoted tubulin polymerization, and the critical tubulin concentration was reduced in the presence of this ***recombinant*** protein. Because a second repeated sequence analogue can promote tubulin polymerization as well as displace the MT-binding region of MAP-2, this study was designed to learn more about the importance of each repeated sequence in MT binding. Accordingly, we mutated the first and third sequences to resemble the second repeated sequence, thereby generating the mutants designed m12-m2-m3, m1-m32, and m12-m2-m32. These ***recombinant*** proteins bound with an affinity comparable to or slightly better than equal concentrations of wild-type MT-binding fragment. Likewise, when the first or third sequence was replaced by an exact copy of the second octadecapeptide repeat, there was little, if any, increase in binding affinity, as reflected in the ability of mutant MT-binding fragments to promote tubulin polymerization.(ABSTRACT TRUNCATED AT 250 WORDS)

(FILE 'HOME' ENTERED AT 10:06:26 ON 18 FEB 97)

FILE 'CAPLUS, BIOSIS, EMBASE, MEDLINE, SCISEARCH, LIFESCI, CANCERLIT' ENTERED AT 10:06:55 ON 18 FEB 97

L1 598 FILE CAPLUS
L2 2566 FILE BIOSIS
L3 1845 FILE EMBASE
L4 1401 FILE MEDLINE
L5 1708 FILE SCISEARCH
L6 739 FILE LIFESCI
L7 270 FILE CANCERLIT
TOTAL FOR ALL FILES
L8 9127 S MTAP OR MICROTUBULE ASSOCIATED PROTEIN
L9 140 FILE CAPLUS
L10 463 FILE BIOSIS
L11 441 FILE EMBASE
L12 341 FILE MEDLINE
L13 506 FILE SCISEARCH
L14 177 FILE LIFESCI
L15 96 FILE CANCERLIT
TOTAL FOR ALL FILES
L16 2164 S L8 AND (CDNA OR EXPRESSION OR RECOMBIN?)
L17 111 FILE CAPLUS
L18 407 FILE BIOSIS
L19 386 FILE EMBASE
L20 298 FILE MEDLINE
L21 453 FILE SCISEARCH
L22 142 FILE LIFESCI
L23 88 FILE CANCERLIT
TOTAL FOR ALL FILES
L24 1885 S L16 AND (EXPRES? OR PURIF?)
L25 3 FILE CAPLUS
L26 15 FILE BIOSIS
L27 22 FILE EMBASE
L28 20 FILE MEDLINE
L29 13 FILE SCISEARCH
L30 5 FILE LIFESCI
L31 4 FILE CANCERLIT
TOTAL FOR ALL FILES
L32 82 S L24 AND (PLASMID# OR VECTOR#)
L33 40 DUP REM L32 (42 DUPLICATES REMOVED)
L34 43 FILE CAPLUS
L35 37 FILE BIOSIS
L36 31 FILE EMBASE
L37 32 FILE MEDLINE
L38 26 FILE SCISEARCH
L39 20 FILE LIFESCI
L40 39 FILE CANCERLIT
TOTAL FOR ALL FILES
L41 228 S MTAP?
L42 4 FILE CAPLUS
L43 1 FILE BIOSIS
L44 2 FILE EMBASE
L45 3 FILE MEDLINE
L46 2 FILE SCISEARCH
L47 4 FILE LIFESCI
L48 0 FILE CANCERLIT

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     TOTAL FOR ALL FILES
L49            16 S L41 AND MICROTUBULE
L50             6 DUP REM L49 (10 DUPLICATES REMOVED)

=>
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L33 ANSWER 3 OF 40 CAPLUS COPYRIGHT 1997 ACS DUPLICATE 1
AN 1997:2871 CAPLUS
DN 126:54544
TI Methylthioadenosine phosphorylase ***cDNA*** transfection alters sensitivity to depletion of purine and methionine in A549 lung cancer cells
AU Hori, Hiroki; Tran, Phuoc; Carrera, Carlos J.; Hori, Yasuko; Rosenbach, Michael D.; Carson, Dennis A.; Nobori, Tsutomu
CS Sam Rose Stein Inst. Res. Aging, Univ. California, San Diego, La Jolla, CA, 92093-0663, USA
SO Cancer Res. (1996), 56(24), 5653-5658
CODEN: CNREA8; ISSN: 0008-5472
DT Journal
LA English
AB Methylthioadenosine phosphorylase (***MTAP***), an enzyme involved in purine and methionine metab., is present in all normal tissues but is frequently deficient in a variety of cancers. It has been suggested that this metabolic difference between normal and cancer cells may be exploited to selectively treat ***MTAP*** -neg. cancers by inhibiting de novo purine synthesis and by depleting L-methionine. However, these therapeutic strategies have only been tested in naturally occurring ***MTAP*** -pos. and -neg. cell lines, which might have addnl. genetic alterations that affect chemotherapeutic sensitivity. Therefore, it is of importance to examine the feasibility of enzyme-selective treatment using paired cell lines that have an identical genotype except for ***MTAP*** status. ***MTAP*** -neg. A549 lung cancer cells were transfected with eukaryotic ***expression*** ***vectors*** encoding ***MTAP*** ***cDNA*** in sense and antisense orientations. The resultant stable transfectomas were treated with inhibitors of de novo purine synthesis such as methotrexate, 5,10-dideazatetrahydrofolate, and L-alanosine and by methionine depletion. The A549 cells transfected with an antisense construct (antisense transfectoma) ***expressed*** no ***MTAP*** protein and were more sensitive to both purine and methionine depletion than were cells ***expressing*** ***MTAP*** protein (sense transfectoma). Methylthioadenosine was able to completely rescue the sense transfectoma but not the antisense transfectoma from growth inhibition by depletion of purine and methionine. These results prove that ***MTAP*** deficiency contributes directly to the sensitivity of cancer cells to purine or methionine depletion. Inhibition of de novo purine synthesis, combined with methionine depletion in the presence of methylthioadenosine, is a highly selective treatment for ***MTAP*** -neg. cancers.

L33 ANSWER 21 OF 40 CAPLUS COPYRIGHT 1997 ACS DUPLICATE 8
AN 1995:229807 CAPLUS
DN 122:7540
TI Localization of specific epitopes on human ***microtubule*** - ***associated*** ***protein*** 2
AU Kalcheva, N.; Albala, J. S.; Binder, L. I.; Shafit-Zagardo, B.
CS Dep. Pathology, Albert Einstein Coll. Med., Bronx, NY, USA
SO J. Neurochem. (1994), 63(6), 2336-41
CODEN: JONRA9; ISSN: 0022-3042
DT Journal
LA English
AB Microtubule-assocd. protein 2 (MAP-2) is an abundant neuronal cytoskeletal protein that binds to tubulin and stabilizes microtubules. Using fusion protein constructs the authors have defined the epitopes of 10 monoclonal antibodies (mAbs) to discrete regions of human MAP-2. Proteins were ***expressed*** in pATH ***vectors*** . After electrophoresis, immunoblotting was performed. By western blot anal. five of the mAbs (AP-14, AP-20, AP-21, AP-23, and AP-25) share epitopes with only the high-mol.-wt. isoforms (MAP-2a, MAP-2b); two of the mAbs (AP-18 and tau 46) recognize MAP-2a, MAP-2b, and MAP-2c. Although AP-18 immunoreactivity was detected within heat-stable protein homogenates isolated from a human neuroblastoma cell line MSN, fusion protein constructs encompassing human MAP-2 were neg., suggesting that the AP-18 epitope is phosphorylated. Furthermore, AP-18 immunoreactivity was lost after alk. phosphatase treatment of heat-stable protein prepns. from MSN cells. Four of the mAbs (322, 636, 635, and 39) recognize epitopes located within amino acids 169-219 of human MAP-2. AP-21 maps to a region between amino acids 553 and 645. AP-23 maps between amino acids 645 and 993, whereas AP-20, AP-14, and AP-25 map between amino acids 995 and 1332. ***Expression*** of the region of MAP-2 between amino acids 1787 and 1824 was pos. to tau 46.

1507 Atzel L14311

L10 ANSWER 40 OF 44 SCISEARCH

AN 87:141170 SCISEARCH

GA The Genuine Article (R) Number: G3533

TI ***MTAP*** DEFICIENCY AND CHROMOSOME-9 IN ACUTE-LEUKEMIA

AU SCALETTI B (Reprint); GRAHAM B H; YOUNG G J; MACKINNON W; GARSON O M; CASTELINO D; VANDERWEYDEN M B

CS ALFRED HOSP, DEPT HEMATOL, PRAHRAN, VIC 3181, AUSTRALIA; ST VINCENTS HOSP, DEPT CYTOGENET, MELBOURNE, VIC, AUSTRALIA

CYA AUSTRALIA

SO AUSTRALIAN AND NEW ZEALAND JOURNAL OF MEDICINE, (1987) Vol. 17, No. 1, pp. 176.

DT Conference; Journal

FS LIFE; CLIN

LA ENGLISH

REC No References

154984

NLM 3/6

1807 Hazel [redacted] 609311

L10 ANSWER 33 OF 44 CAPLUS COPYRIGHT 1997 ACS DUPLICATE 21
AN 1992:509110 CAPLUS
DN 117:109110
TI Molecular genetic analysis of chromosome 9p in methylthioadenosine phosphorylase deficient glioma cell lines
AU Wu, David J.; Reynolds, Linda; Carson, Dennis A.; Nobori, Tsutomu
CS Dep. Med., Univ. California, San Diego, CA, 92093-0945, USA
SO Adv. Exp. Med. Biol. (1991), 309B(Purine Pyrimidine Metab. Man 7, Pt. B), 207-11
CODEN: AEMBAP; ISSN: 0065-2598
DT Journal
LA English
AB Methylthioadenosine (MTA) phosphorylase is the enzyme involved in the metab. of polyamines and purines. MTA, the substrate for this enzyme, is produced during the synthesis of spermine and spermidine and is cleaved to methylthioribose 1-phosphate and adenine, which are recycled to methionine and adenine nucleotide, resp. This enzyme has been known to be deficient in human leukemias, lymphomas, and solid tumors. The gene locus for this enzyme (designated ***MTAP***) has been mapped to human chromosome 9p. Enzyme-deficient malignant cell lines are frequently found to have chromosome 9p abnormalities. Although cytogenetic anal. of human gliomas has demonstrated a very prevalent chromosomal abnormality involving deletions or translocations of chromosome 9p, these tumors have not been tested for ***MTAP*** deficiency. In this report, 8 human glioma cell lines and 6 primary brain tumors were screened for MTA phosphorylase activities by using the radiochem. method and immunoblot anal. Of 14 cell lines and primary tumors, 5 cell lines and 5 primary tumors (70%) were enzyme-deficient. To elucidate the mol. mechanism of this enzyme deficiency and its relevance to the genesis of human brain tumors, DNA anal. and pulsed field gel anal. were carried out.

15 4983

Abl 2/6

NO rl.t

1987 Atzel

L10 ANSWER 43 OF 44 CAPLUS COPYRIGHT 1997 ACS DUPLICATE 27
AN 1984:421160 CAPLUS
DN 101:21160
TI Assignment of the gene for methylthioadenosine phosphorylase to human chromosome 9 by mouse-human somatic cell hybridization
AU Carrera, Carlos J.; Eddy, Roger L.; Shows, Thomas B.; Carson, Dennis A.
CS Dep. Basic Clin. Res., Scripps Clin. Res. Found., La Jolla, CA, 92037, USA
SO Proc. Natl. Acad. Sci. U. S. A. (1984), 81(9), 2665-8
CODEN: PNASA6; ISSN: 0027-8424
DT Journal
LA English
AB To explore the genetic control of methylthioadenosine phosphorylase (I) expression, I levels were measured in somatic cell hybrids prepd. by fusing I-deficient mouse L cell lines with human fibroblasts. In the hybrid clones, I activity segregated concordantly with adenylate kinase 1, a marker for human chromosome 9, but not with enzyme markers for any other human chromosome. In hybrid clones derived from human fibroblasts with a reciprocal translocation between chromosomes 9 and 17, I activity was confined to cells contg. the 9pter.fwdarw.9q12 region. In every case, the I-pos. hybrid clones displayed bands of I activity with pI values characteristic of both the human and murine enzymes. Thus, the structural gene for human I, designated ***MTAP*** , can be assigned to the 9pter.fwdarw.9q12 region of human chromosome 9. Furthermore, these studies with interspecies somatic cell hybrids show that the I-deficient state is recessive in mouse L cell lines.

L10 ANSWER 9 OF 44 SCISEARCH COPYRIGHT 1997 ISI (R)
AN 96:629654 SCISEARCH
GA The Genuine Article (R) Number: VC092
TI EXPLOITATION OF FREQUENT DELETION IN THE METHYLTHIOADENOSINE PHOSPHORYLASE (***MTAP***) GENE IN THE TREATMENT OF T-CELL ACUTE LYMPHOBLASTIC (T-ALL)
AU YU J (Reprint); BATOVA A; SHAO L E; YU A L
CS SCRIPPS CLIN & RES INST, DEPT MOL & EXPT MED, LA JOLLA, CA, 00000; UNIV CALIF SAN DIEGO, DEPT PEDIAT, LA JOLLA, CA, 92093
CYA USA
SO EXPERIMENTAL HEMATOLOGY, (AUG 1996) Vol. 24, No. 9, pp. 544. ISSN: 0301-472X.
DT Conference; Journal
FS LIFE
LA ENGLISH
REC No References

L10 ANSWER 10 OF 44 BIOSIS COPYRIGHT 1997 BIOSIS
AN 96:257612 BIOSIS
DN 98813741
TI Characterization of the methylthioadenosine phosphorylase (***MTAP***) gene product in human cancer: Implications for selective chemotherapy.
AU Pomykala H; Hagos F; Olopade O I
CS Univ. Chicago, Chicago, IL 60637, USA
SO 87th Annual Meeting of the American Association for Cancer Research, Washington, D.C., USA, April 20-24, 1996. Proceedings of the American Association for Cancer Research Annual Meeting 37 (0). 1996. 514. ISSN: 0197-016X
DT Conference
LA English

L10 ANSWER 11 OF 44 BIOSIS COPYRIGHT 1997 BIOSIS
AN 96:256978 BIOSIS
DN 98813107
TI Frequent deletion in the methylthioadenosine phosphorylase (***MTAP***) gene in T-cell acute lymphoblastic leukemia (T-ALL): Strategies for enzyme-targeted therapy.
AU Batova A; Diccianni M B; Nobori T; Vu T; Yu J; Bridgeman L; Yu A L
CS Univ. Calif., San Diego, CA, USA
SO 87th Annual Meeting of the American Association for Cancer Research, Washington, D.C., USA, April 20-24, 1996. Proceedings of the American Association for Cancer Research Annual Meeting 37 (0). 1996. 422. ISSN: 0197-016X
DT Conference
LA English

L10 ANSWER 12 OF 44 BIOSIS COPYRIGHT 1997 BIOSIS
AN 96:256976 BIOSIS
DN 98813105
TI Gene deletion chemoselectivity: Codeletion of the 9p21 genes p16, p15 and 5'-methylthioadenosine phosphorylase (***MTAP***) in malignant cells and its implications for chemotherapy.
AU Chen Z H; Zhang H; Savarese T M
CS Cancer Cent., Univ. Mass. Med. Cent., Worcester, MA 01655, USA
SO 87th Annual Meeting of the American Association for Cancer Research, Washington, D.C., USA, April 20-24, 1996. Proceedings of the American

Association for Cancer Research Annual Meeting 37 (0). 1996. 421.
ISSN: 0197-016X
DT Conference
LA English

L10 ANSWER 13 OF 44 BIOSIS COPYRIGHT 1997 BIOSIS
AN 96:256876 BIOSIS
DN 98813005
TI Toxicity of L-alanosine to ***MTAP*** -deficient cells: Selective treatment strategy for cancer with CDKN2 deletion.
AU Carrera C J; Clason M M; Nobori T; Carson D A
CS UCSD Cancer Cent., Dep. Med., Univ. California San Diego, La Jolla, CA 92093, USA
SO 87th Annual Meeting of the American Association for Cancer Research, Washington, D.C., USA, April 20-24, 1996. Proceedings of the American Association for Cancer Research Annual Meeting 37 (0). 1996. 407.
ISSN: 0197-016X
DT Conference
LA English

L10 ANSWER 14 OF 44 CAPLUS COPYRIGHT 1997 ACS DUPLICATE 7
AN 1996:650410 CAPLUS
DN 125:298402
TI The 9p21 region in bladder cancer cell lines: Large homozygous deletions inactivate the CDKN2, CDKN2B and ***MTAP*** genes
AU Stadler, W. M.; Olopade, O. I.
CS Department Medicine, University Chicago, Chicago, IL, 60637, USA
SO Urol. Res. (1996), 24(4), 239-244
CODEN: URLRA5; ISSN: 0300-5623
DT Journal
LA English
AB Homozygous and hemizygous deletions of 9p21 are the earliest and most common genetic alteration in bladder cancer. The identification of two cell cycle regulators, CDKN2 and CDKN2B, that map to the common region of deletion has prompted the hypothesis that they are crit. tumor suppressor genes in this malignancy. However, controversy as to whether these genes are the only or even the most important target in bladder cancer oncogenesis remains. To more clearly det. the effect of these 9p21 alterations, the authors mapped the homozygous deletions and performed a detailed mutational and expression anal. for CDKN2, CDKN2B and a closely linked gene, methylthioadenosine phosphorylase (***MTAP***), in 16 established bladder cancer cell lines. Nine of the 16 lines exhibit large (30 to >2000 kb) homozygous deletions on 9p21. All deletions include at least one exon of CDKN2, eight of nine include CDKN2B, and six of nine include ***MTAP*** . ***MTAP*** function correlates with the genomic deletions. SSCP and sequence anal. does not reveal any inactivating point mutations of CDKN2 or of CDKN2B in any of the cell lines without homozygous deletions, and all express the CDKN2 and the CDKN2B mRNA as well as the encoded p16 protein. The p16 protein levels vary widely and are correlated with absent pRb expression. The authors conclude that the 9p21 deletions in bladder cancer usually inactivate the CDKN2, CDKN2B, and ***MTAP*** genes but that CDKN2 is the most common target. Other mechanisms for inactivating this gene in bladder cancer appear to be uncommon.

L10 ANSWER 15 OF 44 CAPLUS COPYRIGHT 1997 ACS DUPLICATE 8

(FILE 'HOME' ENTERED AT 13:44:38 ON 05 FEB 97)

FILE 'CAPLUS, MEDLINE, BIOSIS, EMBASE, INPADOC, DISSABS, SCISEARCH, LIFESCI' ENTERED AT 13:45:15 ON 05 FEB 97

L1	31	FILE CAPLUS
L2	25	FILE MEDLINE
L3	30	FILE BIOSIS
L4	25	FILE EMBASE
L5	0	FILE INPADOC
L6	1	FILE DISSABS
L7	21	FILE SCISEARCH
L8	15	FILE LIFESCI
		TOTAL FOR ALL FILES
L9	148	S MTAP
L10	44	DUP REM L9 (104 DUPLICATES REMOVED)

=>

L10 ANSWER 1 OF 44 CAPLUS COPYRIGHT 1997 ACS
AN 1997:76072 CAPLUS
TI Molecular cloning of the human methylthioadenosine phosphorylase processed pseudogene and localization to 3q28
AU Tran, Phuoc T.; Hori, Hiroki; Hori, Yasuko; Okumura, Katsuzumi; Kazuhiro Kagotani; Taguchi, Hiroshi; Carson, Dennis A.; Nobori, Tsutomu
CS Department of Medicine, University of California, San Diego, La Jolla, CA, 92093-0663, USA
SO Gene (1997), 186(2), 263-269
CODEN: GENED6; ISSN: 0378-1119
DT Journal
LA English
AB Human methylthioadenosine phosphorylase (***MTAP***) is a purine and methionine metabolic enzyme present ubiquitously in all normal tissues, but often deleted in many types of cancer. The gene for this enzyme maps to chromosome 9 at band p21 where the cyclin-dependent kinase inhibitor genes for p16 and p15 also reside. During our efforts to clone this gene we also isolated a phage clone contg. a processed pseudogene of ***MTAP*** . The sequence is 92 homologous to the ***MTAP*** cDNA, is flanked at its 3′ end by a repetitive element, but does not possess a poly(A) stretch. We localized this processed pseudogene to band 28 on the long arm of chromosome 3 by fluorescence in situ hybridization. All 22 malignant cell lines with deletions at 9p21 screened possessed the pseudogene.

L10 ANSWER 2 OF 44 CAPLUS COPYRIGHT 1997 ACS DUPLICATE 1
AN 1996:367069 CAPLUS
DN 125:134076
TI Genomic cloning of methylthioadenosine phosphorylase: a purine metabolic enzyme deficient in multiple different cancers
AU Nobori, Tsutomu; Takabayashi, Kenji; Tran, Phuoc; Orvis, Lisa; Batova, Ayse; Yu, Alice L.; Carson, Dennis A.
CS Sam and Rose Stein Inst. Res. Aging, Univ. California, San Diego, La Jolla, CA, 92093-0663, USA
SO Proc. Natl. Acad. Sci. U. S. A. (1996), 93(12), 6203-6208
CODEN: PNASA6; ISSN: 0027-8424
DT Journal
LA English
AB 5′-Deoxy-5′-methylthioadenosine phosphorylase (methylthioadenosine: ortho-phosphate methylthioribosyltransferase, EC 24.2.28; ***MTAP***) plays a role in purine and polyamine metab. and in the regulation of transmethylation reactions. ***MTAP*** is abundant in normal cells but is deficient in many cancers. Recently, the genes for the cyclin-dependent kinase inhibitors p16 and p15 have been localized to the short arm of human chromosome 9 at band p21, where ***MTAP*** and interferon .alpha. genes (IFNA) also map. Homozygous deletions of p16 and p15 are frequent in malignant cell lines. However, the order of the ***MTAP*** , p16, p15, and IFNA genes on chromosome 9p is uncertain, and the mol. basis for ***MTAP*** deficiency in cancer is unknown. We have cloned the ***MTAP*** gene, and have constructed a topol. map of the 9p21 region using yeast artificial chromosome clones, pulse-field gel electrophoresis, and sequence-tagged-site PCR. The ***MTAP*** gene consists of eight exons and seven introns. Of 23 malignant cell lines deficient in ***MTAP*** protein, all but

one had complete or partial deletions. Partial or total deletions of the ***MTAP*** gene were found in primary T-cell acute lymphoblastic leukemias (T-ALL). A deletion breakpoint of partial deletions found in cell lines and primary T-ALL was in intron 4. Starting from the centromeric end, the gene order on chromosome 9p21 is p15, p16, ***MTAP*** , IFNA, and interferon .beta. gene (IFNB). These results indicate that ***MTAP*** deficiency in cancer is primarily due to codeletion of the ***MTAP*** and p16 genes.

L10 ANSWER 3 OF 44 CAPLUS COPYRIGHT 1997 ACS DUPLICATE 2
AN 1997:2871 CAPLUS
DN 126:54544
TI Methylthioadenosine phosphorylase cDNA transfection alters sensitivity to depletion of purine and methionine in A549 lung cancer cells
AU Hori, Hiroki; Tran, Phuoc; Carrera, Carlos J.; Hori, Yasuko; Rosenbach, Michael D.; Carson, Dennis A.; Nobori, Tsutomu
CS Sam Rose Stein Inst. Res. Aging, Univ. California, San Diego, La Jolla, CA, 92093-0663, USA
SO Cancer Res. (1996), 56(24), 5653-5658
CODEN: CNREA8; ISSN: 0008-5472
DT Journal
LA English
AB Methylthioadenosine phosphorylase (***MTAP***), an enzyme involved in purine and methionine metab., is present in all normal tissues but is frequently deficient in a variety of cancers. It has been suggested that this metabolic difference between normal and cancer cells may be exploited to selectively treat ***MTAP*** -neg. cancers by inhibiting de novo purine synthesis and by depleting L-methionine. However, these therapeutic strategies have only been tested in naturally occurring ***MTAP*** -pos. and -neg. cell lines, which might have addnl. genetic alterations that affect chemotherapeutic sensitivity. Therefore, it is of importance to examine the feasibility of enzyme-selective treatment using paired cell lines that have an identical genotype except for ***MTAP*** status. ***MTAP*** -neg. A549 lung cancer cells were transfected with eukaryotic expression vectors encoding ***MTAP*** cDNA in sense and antisense orientations. The resultant stable transfectomas were treated with inhibitors of de novo purine synthesis such as methotrexate, 5,10-dideazatetrahydrofolate, and L-alanosine and by methionine depletion. The A549 cells transfected with an antisense construct (antisense transfectoma) expressed no ***MTAP*** protein and were more sensitive to both purine and methionine depletion than were cells expressing ***MTAP*** protein (sense transfectoma). Methylthioadenosine was able to completely rescue the sense transfectoma but not the antisense transfectoma from growth inhibition by depletion of purine and methionine. These results prove that ***MTAP*** deficiency contributes directly to the sensitivity of cancer cells to purine or methionine depletion. Inhibition of de novo purine synthesis, combined with methionine depletion in the presence of methylthioadenosine, is a highly selective treatment for ***MTAP*** -neg. cancers.

L10 ANSWER 4 OF 44 CAPLUS COPYRIGHT 1997 ACS DUPLICATE 3
AN 1996:631074 CAPLUS
DN 125:267272

TI Frequent deletion in the methylthioadenosine phosphorylase gene in T-cell acute lymphoblastic leukemia: strategies for enzyme-targeted therapy

AU Batova, Ayse; Diccianni, Mitchell B.; Nobori, Tsutomu; Vu, Thai; Yu, John; Bridgeman, Louis; Yu, Alice L.

CS Univ. California San Diego, San Diego, CA, USA

SO Blood (1996), 88(8), 3083-3090
CODEN: BLOOAW; ISSN: 0006-4971

DT Journal

LA English

AB Methylthioadenosine phosphorylase (***MTAP***), an enzyme essential for the salvage of adenine and methionine, is deficient in a variety of cancers, including acute lymphoblastic leukemia (ALL). Because the ***MTAP*** gene is located adjacent to the tumor-suppressor gene p16 on chromosome 9p21 and more than 60% of T-cell ALL (T-ALL) patients have deletion in the p16 gene, we examd. the status of the ***MTAP*** gene in T-ALL patients. Quant. polymerase chain reaction amplification of exon 8 of ***MTAP*** showed a deletion in 16 of 48 (33.3%) patients at diagnosis and in 13 of 22 (39.4%) patients at relapse. Southern blot anal. showed that, in addn. to deletion of the entire ***MTAP*** gene, a common break point was between exons 4 and 5, resulting in deletion of exons 5 through 8. The finding of frequent deficiency of ***MTAP*** in T-ALL offers the possibility of an enzyme targeted therapy for T-ALL. ***MTAP*** (-) T-ALL-derived cell line, CEM cells were very sensitive to methionine deprivation, with cell viability at 50% of control as early as 48 h after methionine deprivation. In contrast, methionine deprivation had little effect on the viability of normal lymphocytes or on their proliferative response to phytohemagglutinin. Alanosine, an inhibitor of AMP synthesis, inhibited the growth of both ***MTAP*** (+) (Molt-4 and Molt-16) and ***MTAP*** (-) (9CEM and HSB2) cell lines. Alanosine, an inhibitor of AMP synthesis, inhibited the growth of both ***MTAP*** (+) (Molt-4 and Molt-16) and ***MTAP*** (-) (9CEM and HSB2) cell lines. However, the addn. of methylthioadenosine, the substrate of ***MTAP*** , protected the ***MTAP*** (+) cells but not the ***MTAP*** (-) cells from alanosine toxicity. These findings suggest the possibility of targeting ***MTAP*** for selective therapy of T-ALL.

L10 ANSWER 6 OF 44 BIOSIS COPYRIGHT 1997 BIOSIS
AN 96:451051 BIOSIS
DN 99173407
TI Exploitation of frequent deletion in the methylthioadenosine phosphorylase (***MTAP***) gene in the treatment of T-cell acute lymphoblastic leukemia (T-ALL).
AU Yu J; Batova A; Shao L E; Yu A L
CS Dep. Mol. Exp. Med., Scripps Res. Inst., UCSD, La Jolla, CA, USA
SO 25th Annual Meeting of the International Society for Experimental Hematology, New York, New York, USA, August 23-27, 1996. Experimental Hematology (Charlottesville) 24 (9). 1996. 1124. ISSN: 0301-472X
DT Conference
LA English

L10 ANSWER 7 OF 44 CAPLUS COPYRIGHT 1997 ACS DUPLICATE 5
AN 1996:136741 CAPLUS
DN 124:219727
TI Gene deletion chemoselectivity: co-deletion of the genes for p16INK4 methylthioadenosine phosphorylase, and the .alpha.- and .beta.-interferons in human pancreatic cell carcinoma lines and its implications for chemotherapy
AU Chen, Zhi-Hao; Zhang, Hongyang; Savarese, Todd M.
CS Cancer Cent., Univ. Massachusetts Med. Cent., Worcester, MA, 01655, USA
SO Cancer Res. (1996), 56(5), 1083-90
CODEN: CNREA8; ISSN: 0008-5472
DT Journal
LA English
AB Pancreatic carcinoma cells lines are known to have a high incidence of homozygous deletion of the candidate tumor suppressor gene p16 (MTS1/CDKN2), which resides in the chromosome 9p21 region. Here we: (a) examd. a series of these cell lines for the incidence of co-deletion of genes located near p16, in particular, the gene for the enzyme 5'-deoxy-5'-methylthioadenosine phosphorylase (***MTAP***) and the genes of the IFN-.alpha. and -.beta. cluster (IFNs); and (b) investigated whether therapeutic strategies could be developed that target malignant cells that have undergone the co-deletion of such genes. Five of the eight pancreatic carcinoma cell lines were p16-, ***MTAP*** was co-deleted in all five cases. Because ***MTAP*** phosphorolyzes 5'-deoxy-5'-methylthioadenosine (MTA), generated as a byproduct of polyamine synthesis, to the salvageable purine base adenine, loss of this pathway in p16-, ***MTAP*** - cells might sensitize these cells to methotrexate (MTX), the mechanism of action of which involves, in part, an inhibition of purine de novo synthesis. ***MTAP*** + normal keratinocytes and pancreatic carcinoma lines had relatively poor sensitivity, in terms of efficacy, to the purine nucleotide-starving actions of MTX. This may be in part due to the ***MTAP*** -dependent salvage of adenine moieties from endogenously generated MTA, because the ***MTAP*** inhibitor 5'-chloro-5'-deoxyformycin A potentiates the antipurine actions of MTX in some of these ***MTAP*** + lines. Also, exogenous MTA (10 .mu.M) reverses the growth-inhibitory actions of MTX in these lines. In contrast, ***MTAP*** - cell lines, which cannot recycle purines from endogenous MTA, have a relatively high sensitivity to the antipurine actions of MTX, which is not modulated by 5'-chloro-5'-deoxyformycin A or exogenous MTA. Thus the

MTAP loss in malignant cells may be an example of gene deletion chemoselectivity, in which genetic deletions that occur as part of the oncogenic process render these cells more sensitive to particular anticancer agents than normal cells, which have not undergone such deletions. We also examd. whether the loss of IFN genes sensitize cells to the growth-inhibitory actions of these cytokines. Three of the five p16- cell lines bore homozygous deletions of IFNA1 and IFNB1 genes, representing each end of the IFN-.alpha.,-.beta. gene cluster; one cell line bore a co-deletion of the IFNA1 gene but retained the IFNB1 locus. Whereas the cell lines that were most sensitive to the growth-inhibitory effects of IFN-.beta. or IFN-.alpha.2b tended to be those with IFN deletions, there were enough exceptions to this pattern to indicate that the IFN genotype does not reliably predict IFN responsiveness.

L10 ANSWER 8 OF 44 CAPLUS COPYRIGHT 1997 ACS DUPLICATE 6
AN 1996:421205 CAPLUS
DN 125:83336
TI p16INK4A gene homozygous deletions in human acute leukemias with alterations of chromosome 9
AU Faienza, Maria Felicia; Ragione, Fulvio Della; Basso, Guiseppe; Coppola, Brigida; Del Giudice, Emanuele Miraglia; Schettini, Francesco; Iolascon, Achille
CS Dipartimento di Biomedicina dell'Eta Evolutive, Universita di Bari, Bari, 70124, Italy
SO Br. J. Haematol. (1996), 93(3), 632-636
CODEN: BJHEAL; ISSN: 0007-1048
DT Journal
LA English
AB Acute leukemias are characterized by nonrandom chromosomal aberrations which are often strictly related to the inactivation of tumor suppressor genes (TSGs). Alterations at the short arm of chromosome 9 have been reported in a remarkable percentage of acute lymphoblastic leukemias (ALL) and have been suggested to cause the loss of activity of the putative TSG, p16INK4A (MTS1/CDKN2) gene. To evaluate the correlation between this gene inactivation and visible cytogenetic abnormalities, the authors have investigated p16INK4A homozygous gene deletions in 10 pediatric acute leukemias of different cell lineages which demonstrated karyotype aberrations involving chromosome 9. Moreover, the dimension of the genetic alteration was evaluated by studying the loss of heterozygosity of two highly polymorphic markers of chromosome 9p, namely .alpha.-interferon (IFNA) and D9S104, and the deletion of 5'-methylthioadenosine phosphorylase (MTAPase) gene. Finally, the deletion of a gene belonging to p16INK4A family, the p18 gene, was analyzed in these acute leukemias. The authors' results demonstrated that: (i) the biallelic loss of p16INK4A gene is strictly related to a specific immunophenotype, namely ALL of T-cell lineage; (ii) no significant correlation exists between alterations at chromosome 9p level and the homozygous deletions of p16INK4A gene; and (iii) p18 gene was not deleted in the examd. cases. These findings suggest a possible correlation between the T-lymphocyte phenotype and the expression of p16INK4A gene. Moreover, the absence of MTAPase activity seems to be a valuable marker of p16INK4A gene inactivation, thus indicating that the deleted chromosomal area on 9p21 very frequently involves the MTAPase gene.

AN 1996:465863 CAPLUS
DN 125:139319
TI Chromosome 9 related aberrations and deletions of the CDKN2 and MTS2 putative tumor suppressor genes in human chondrosarcomas
AU Jagasia, Ashok A.; Block, Joel A.; Qureshi, Abid; Diaz, Manuel O.; Nobori, Tsutomu; Gitelis, Steven; Iyer, Anand P.
CS Div. Hematol./Oncol., Loyola Univ. Med. Cent., Maywood, IL, 60153, USA
SO Cancer Lett. (Shannon, Irel.) (1996), 105(1), 91-103
CODEN: CALEDQ; ISSN: 0304-3835
DT Journal
LA English
AB Deletions on the short arm of chromosome 9 (9p21 region) have been reported in a no. of hematopoietic and solid tumors. These aberrations on 9p have been previously assocd. with the loss of the interferon gene cluster and the gene for methylthioadenosine phosphorylase (***MTAP***), localized to the 9p21-22 region. Recently, two putative tumor suppressor gene(s) CDKN2 and MTS2 have been mapped to the 9p21 region, and shown to be deleted in a large no. of tumors including leukemias, melanomas, bladder cancers and brain tumors. The authors have previously reported a similar 9p21 abnormality and deletions of the CDKN2 and MTS2 genes in a myxoid chondrosarcoma cell line and its subclones. In this study the authors report consistent abnormalities of chromosome 9 in addnl. chondrosarcomas examd. by a detailed cytogenetic and mol. anal. Seven chondrosarcoma cell lines, one primary chondrosarcoma, and a benign chondroma were examd. Four of the seven tumor cell lines examd. showed grossly visible aberrations of chromosome 9. Mol. anal. of these chondrosarcoma cell lines revealed hemizygous deletions of the interferon genes, and the absence of the ***MTAP*** gene, protein or activity. In addn., four of the seven chondrosarcoma cell lines also showed deletions of the CDKN2 and/or MTS2 putative tumor suppressor genes, or the absence of the CDKN2 protein product. No such chromosome 9 related aberrations were detected in the benign chondroma. These data suggest that chromosome 9p21 abnormality, and deletions of the CDKN2 and MTS2 tumor suppressor genes may be a significant event in the development of chondrosarcomas.

L10 ANSWER 16 OF 44 CAPLUS COPYRIGHT 1997 ACS DUPLICATE 9
AN 1996:465862 CAPLUS
DN 125:139318
TI Partial deletions of the CDKN2 and MTS2 putative tumor suppressor genes in a myxoid chondrosarcoma
AU Jagasia, Ashok A.; Block, Joel A.; Diaz, Manuel O.; Nobori, Tsutomu; Gitelis, Steven; Inerot, Sven E.; Iyer, Anand P.
CS Div. Hematology/Oncol., Loyola Univ. Med. Cent., Maywood, IL, 60153, USA
SO Cancer Lett. (Shannon, Irel.) (1996), 105(1), 77-90
CODEN: CALEDQ; ISSN: 0304-3835
DT Journal
LA English
AB Cytogenetic abnormalities of chromosome 9 (9p21) have been reported in a large no. of tumors that include malignant melanomas, gliomas, lung cancers and leukemias. These aberrations on 9p have been previously shown to involve the loss of the interferon gene cluster and the gene for methylthioadenosine phosphorylase (***MTAP***), both of which have been mapped to the 9p21 region. Recently, two

putative tumor suppressor gene(s) CDKN2 and MTS2, have been mapped to the 9p21 region, and have been shown to be deleted in a large no. of hematopoietic and solid malignancies. In this study the authors report a cytogenetic and a detailed mol. anal. of a myxoid chondrosarcoma cell line 105KC and its clonal derivs. 105AJ, 105AJ1.1, 105AJ3.1, and 105AJ5.1. Specifically, the authors have demonstrated chromosome 9p21 related abnormalities by cytogenetic anal., the assocd. loss of the interferon gene cluster, and the loss of the immunoreactive ***MTAP*** protein and activity. In addn., the authors have also shown the presence of deletions involving the CDKN2 and the MTS2 putative tumor suppressor genes in these chondrosarcoma cell lines. The above studies were extended to other chondrosarcoma cell lines and primary tumors, where similar deletions of the CDKN2 and MTS2 genes were present (unpublished data). This suggests a potential role for the involvement of the CDKN2 and MTS2 putative tumor suppressor genes in the development of chondrosarcomas.

L10 ANSWER 17 OF 44 LIFESCI COPYRIGHT 1997 CSA
AN 96:111181 LIFESCI
TI Partial deletions of the CDKN2 and MTS2 putative tumor suppressor genes in a myxoid chondrosarcoma
AU Jagasia, A.A.; Block, J.A.; Diaz, M.O.; Nobori, T.; Gitelis, S.; Inerot, S.E.; Iyer, A.P.
CS Div. Hematol./Oncol., Dep. Med., Loyola Univ. Med. Cent., Maywood, IL 60153, USA
SO CANCER LETT., (1996) vol. 105, no. 1, pp. 71-90.
ISSN: 0304-3835.
DT Journal
FS G
LA English
SL English
AB Cytogenetic abnormalities of chromosome 9 (9p21) have been reported in a large number of tumors that include malignant melanomas, gliomas, lung cancers and leukemias. These aberrations on 9p have been previously shown to involve the loss of the interferon gene cluster and the gene for methylthioadenosine phosphorylase (***MTAP***), both of which have been mapped to the 9p21 region. Recently, two putative tumor suppressor gene(s) CDKN2 and MTS2, have been mapped to the 9p21 region, and have been shown to be deleted in a large number of hematopoietic and solid malignancies. In this study we report a cytogenetic and a detailed molecular analysis of a myxoid chondrosarcoma cell line 105KC and its clonal derivatives 105AJ, 105AJ1.1, 105AJ3.1, and 105AJ5.1. Specifically, we have demonstrated chromosome 9p21 related abnormalities by cytogenetic analysis, the associated loss of the interferon gene cluster, and the loss of the immunoreactive ***MTAP*** protein and activity. In addition, we have also shown the presence of deletions involving the CDKN2 and the MTS2 putative tumor suppressor genes in these chondrosarcoma cell lines. The above studies were extended to other chondrosarcoma cell lines and primary tumors, where similar deletions of the CDKN2 and MTS2 genes were found to be present (unpublished data). This suggests a potential role for the involvement of the CDKN2 and MTS2 putative tumor suppressor genes in the development of chondrosarcomas.

L10 ANSWER 18 OF 44 CAPLUS COPYRIGHT 1997 ACS DUPLICATE 10
AN 1996:208607 CAPLUS

DN 124:257147
TI Codeletion of the genes for p16INK4, methylthioadenosine phosphorylase, interferon-.alpha.1, interferon-.beta.1, and other 9p21 markers in human malignant cell lines
AU Zhang, Hongyang; Chen, Zhi-Hao; Savarese, Todd M.
CS Cancer Center, University Massachusetts, Worcester, MA, 01655, USA
SO Cancer Genet. Cytogenet. (1996), 86(1), 22-8
CODEN: CGCYDF; ISSN: 0165-4608
DT Journal
LA English
AB In this study, 27 malignant cell lines, including leukemias, gliomas, and lung and bladder carcinomas were screened for homozygous deletions of the putative tumor suppressor gene p16 (MTS1/CDK4I/CDKN2) and other markers within the chromosome 9p21 region; these include the genes for interferon-.alpha.1 (IFNA1), interferon-.beta.1 (IFNB1), methylthioadenosine phosphorylase (***MTAP***), and two microsatellite markers, D9S171 and D9S169. The purpose of this study was to det. the incidence of co-deletion of these markers. Screening for homozygous deletions was carried out using direct polymerase chain reaction of genomic DNA, or, in the case of ***MTAP*** , a functional enzyme assay. Of these cell lines, 14 (52%) were found to have homozygous deletions of the p16 gene. Two of the 14 p16-neg. cell lines (14%) were found to have homozygous deletions within the p16 domain but no other 9p21 marker. ***MTAP*** was co-deleted in 12 of the 14 p16-neg. cell lines (86%), whereas IFNA1 was co-deleted with p16 in eight of these lines (57%); IFNB1 was co-deleted in five (36%) of the p16-deleted cell lines. The D9S171 marker, which may lie greater than 3 cM centromeric to p16, is co-deleted in three cell lines (21%); the D9S169 marker, which maps even further toward the centromere, was co-deleted in only one cell line (7%). Loss of any 9p21 marker, e.g., ***MTAP*** or IFNA1, were invariable predictors of the loss of the p16 gene. In addn., loss of IFNA1 always predicted a loss of ***MTAP*** (eight of eight cell lines), although loss of ***MTAP*** did not always predict a loss of IFNA1 (four of 12 ***MTAP*** -deleted cell lines did not have homozygous deletions of IFNA1). Thus loss of nearby genes occurs in a high percentage of cell lines that bear homozygous deletions of the p16 locus. Co-deletion of ***MTAP*** or IFN in p16-neg. malignant cells is of interest, as loss of these genes may influence the biol. behavior of these cells and render them susceptible to certain therapeutic approaches.

L10 ANSWER 19 OF 44 CAPLUS COPYRIGHT 1997 ACS DUPLICATE 11
AN 1995:676996 CAPLUS
DN 123:248063
TI Construction of a 2.8-megabase yeast artificial chromosome contig and cloning of the human methylthioadenosine phosphorylase gene from the tumor suppressor region on 9p21
AU Olopade, Olufunmilayo I.; Pomykala, Helen M.; Hagos, Fitsum; Sveen, Lise W.; Espinosa, Rafael, III; Dreyling, Martin H.; Gursky, Susan; Stadler, Walter M.; Le Beau, Michelle M.; Bohlander, Stefan K.
CS Section Hematol./Oncol., Univ. Chicago Pritzker Sch. Med., Chicago, IL, 60637, USA
SO Proc. Natl. Acad. Sci. U. S. A. (1995), 92(14), 6489-93
CODEN: PNASA6; ISSN: 0027-8424
DT Journal
LA English
AB Many human malignant cells lack methylthioadenosine phosphorylase (***MTAP***) enzyme activity. The gene (***MTAP***) encoding this enzyme was previously mapped to the short arm of chromosome 9, band p21-22, a region that is frequently deleted in multiple tumor types. To clone candidate tumor suppressor genes from the deleted region on 9p21-22, a long-range phys. map of 2.8 megabases was constructed for 9p21 by using overlapping yeast artificial chromosome and cosmid clones. This map includes the type I IFN gene cluster, the recently identified candidate tumor suppressor genes CDKN2 (p16INK4A) and CDKN2B (p15INK4B), and several CpG islands. In addn., other transcription units were identified within the yeast artificial chromosome contig. Sequence anal. of a 2.5-kb cDNA clone isolated from a CpG island that maps between the IFN genes and CDKN2 reveals a predicted open reading frame of 283 amino acids followed by 1302 nucleotides of 3′ untranslated sequence. This gene is evolutionarily conserved and shows significant amino acid homologies to mouse and human purine nucleoside phosphorylases and to a hypothetical 25.8-kDa protein in the pet gene (coding for cytochrome bc1 complex) region of Rhodospirillum rubrum. The location, expression pattern, and nucleotide sequence of this gene suggest that it codes for the ***MTAP*** enzyme.

L10 ANSWER 20 OF 44 CAPLUS COPYRIGHT 1997 ACS DUPLICATE 12
AN 1995:776896 CAPLUS
DN 123:166459
TI Refined mapping of genomic rearrangements involving the short arm of chromosome 9 in acute lymphoblastic leukemias and other hematologic malignancies
AU Dreyling, M. H.; Bohlander, S. K.; Le Beau, M. M.; Olopade, O. I.
CS Dep. of Medicine, Univ. of Chicago, Chicago, IL, USA
SO Blood (1995), 86(5), 1931-8
CODEN: BLOOAW; ISSN: 0006-4971
DT Journal
LA English
AB Deletions of chromosomal band 9p21 have been detected in various tumor types as well as in more than 20% of acute lymphoblastic leukemia (ALL). These deletions frequently include the entire interferon (IFN) gene cluster as well as the methylthioadenosine phosphorylase (***MTAP***) gene. Recently, the CDKN2 gene (p16INK4A, MTS I, CDK4I) was proposed as a candidate tumor-suppressor gene on 9p21 because it is frequently deleted in cell lines derived from multiple tumor types. To det. if CDKN2 or

another closely related gene on 9p is the target of 9p deletions in ALL and other hematol. malignancies, the authors analyzed 20 primary patient samples (13 ALL, 2 acute myeloid leukemias [AML], and 5 non-Hodgkin's lymphomas [NHL]) with 9p rearrangements using Southern blot anal., fluorescence in situ hybridization (FISH), and single-strand conformation polymorphism (SSCP) for alterations of CDKN2. Homozygous deletions of the CDKN2/CDKN2B (p15) region were detected in 10 cases (50%; 6 ALL, 2 AML, and 2 NHL). In 1 addnl. case, the intensity of the Southern blot band was significantly reduced, suggesting a CDKN2 deletion in a subpopulation of the malignant cells. No CDKN2 or CDKN2B rearrangements were seen. The IFN gene cluster was homozygously deleted in 2 of 15 (13%) analyzed cases, whereas the ***MTAP*** gene was deleted in 6 of 15 cases (40%). In addn., hemizygous deletions of the CDKN2 region were identified in 6 ALL cases using interphase FISH. No point mutation of the coding region of CDKN2 was detected by SSCP in these cases. The authors conclude that CDKN2 is the most frequently homozygously deleted marker on 9p. The absence of point mutations in the coding region of CDKN2 in cases with hemizygous 9p deletions and the frequent co-deletion of ***MTAP*** , CDKN2B, and other yet unidentified neighboring genes suggest that the simultaneous deletion of these genes may be necessary for the selective growth advantages of malignant cells.

L10 ANSWER 22 OF 44 CAPLUS COPYRIGHT 1997 ACS DUPLICATE 13
AN 1994:317044 CAPLUS
DN 120:317044
TI Homozygous deletions within chromosomal bands 9p21-22 in bladder cancer
AU Stadler, Walter M.; Sherman, Jeniffer; Bohlander, Stefan K.; Roulston, Diane; Dreyling, Martin; Rukstalis, Daniel; Olopade, Olufunmilayo I.
CS Sect. Hematol., Univ. Chicago, Chicago, IL, 60637, USA
SO Cancer Res. (1994), 54(8), 2060-3
CODEN: CNREA8; ISSN: 0008-5472
DT Journal
LA English
AB The loss of DNA sequences on chromosomal bands 9p21-22 has been documented in a variety of malignancies including leukemias, gliomas, lung cancers, and melanomas. Because of the high incidence of monosomy 9 detected by both cytogenetics and loss of heterozygosity studies in bladder cancer, the authors examd. seven bladder cancer cell lines for deletions in this region. Using seven DNA probes that span the region of 9p21-22 as well as a functional assay for methylthioadenosine phosphorylase (***MTAP***), which maps to 9p21, the authors found four cell lines that had small homozygous deletions. These deletions map centromeric to the interferon (IFN) gene cluster and telomeric to D9S171. Only one of the cell lines with deletions had a cytogenetically evident lesion in this chromosomal region. Preliminary loss of heterozygosity studies with 10 primary bladder cancer specimens using 10 markers spanning chromosome 9 revealed loss of heterozygosity at the IFn locus with retention of heterozygosity with more centromeric 9p markers and all informative 9q markers in the tumor of one patient. These data suggest that loss of a tumor suppressor gene on 9p21-22, which may represent a general pathway of oncogenesis, is important in bladder cancer development.

L10 ANSWER 23 OF 44 CAPLUS COPYRIGHT 1997 ACS
AN 1995:936469 CAPLUS
DN 124:26143
TI Myocardial 5'deoxy-5'methylthioadenosine phosphorylase
AU Ruckemann, Katarzyna; Jagodzinski, Piotr; Smolenski, Ryszard T.
CS Department Biochemistry, Academic Medical School Gdansk, Gdansk, 80-211, Pol.
SO Adv. Exp. Med. Biol. (1994), 370(Purine and Pyrimidine Metabolism in Man VIII), 537-9
CODEN: AEMBAP; ISSN: 0065-2598
DT Journal
LA English
AB The activity of 5'-deoxy-5'-methylthioadenosine phosphorylase (***MTAP***) was measured in homogenates of rat and human hearts as well as in cardiomyocytes isolated from the rat heart using the collagenase perfusion technique and was compared to the purine nucleoside phosphorylase (PNP) activity. Substantial ***MTAP*** activity was obsd. in the heart. This activity was esp. high in the human heart, whereas the opposite was shown for PNP. Almost half of the myocardial activity of ***MTAP*** was located in myocytes, whereas the contribution of these cells to total heart PNP was only several percent.

L10 ANSWER 24 OF 44 CAPLUS COPYRIGHT 1997 ACS DUPLICATE 14
AN 1995:346238 CAPLUS
DN 122:129926
TI Analysis of tumor suppressor gene on human chromosome 9 in mouse .times. human somatic cell hybrids
AU Porterfield, Bruce W.; Olopade, Olufunmilayo I.; Rowley, Janet D.; Diaz, Manuel O.
CS Div. Biol. Sci., Univ. Chicago, Chicago, IL, 60637, USA
SO Somatic Cell Mol. Genet. (1994), 20(5), 391-400
CODEN: SCMGDN; ISSN: 0740-7750
DT Journal
LA English
AB Deletions of the short arm of human chromosome 9 (9p) are common in human leukemia and solid tumors. The min. region of overlap of these deletions, located between the interferon genes and the methylthioadenosine phosphorylase gene, is partially syntenic with a region of mouse chromosome 4 that has tumor suppressor activity. Somatic cell hybrids between tumorigenic, ***MTAP*** -deficient, mouse L cells, and ***MTAP*** -competent human cells contg. either a normal copy of 9p or 9p with a deletion involving band 9p21 were selected in culture conditions that require ***MTAP*** activity for continued growth. Somatic cell hybrids that contained a normal copy of 9p rarely formed tumors in nude mice. Cells from the rare tumors that grew had lost the normal 9p. Hybrid cells that contained a 9p with deletions formed tumors more frequently, and cells from these tumors retained the 9p deletion chromosome. These results provide evidence that a tumor suppressor gene (or genes) is located on human chromosome 9 within the region of deletion.

L10 ANSWER 26 OF 44 CAPLUS COPYRIGHT 1997 ACS DUPLICATE 15
AN 1993:470215 CAPLUS
DN 119:70215
TI Homozygous loss of the interferon genes defines the critical region on 9p that is deleted in lung cancers
AU Olopade, Olufunmilayo I.; Buchhagen, Dorothy L.; Malik, Kathleen; Sherman, Jennifer; Nobori, Tsutomu; Bader, Scott; Nau, Marion M.; Gazdar, Adi F.; Minna, John D.; Diaz, Manuel O.
CS Dep. Med., Univ. Chicago, Chicago, IL, 60637, USA
SO Cancer Res. (1993), 53(10), 2410-15
CODEN: CNREA8; ISSN: 0008-5472
DT Journal
LA English
AB Cytogenetic analyses of non-small cell lung cancer have revealed deletions of the short arm of chromosome 9 with breakpoints at 9p11-pter in a significant proportion of tumors. Recent evidence suggests that homozygous loss of the interferon (IFN) and methylthioadenosine phosphorylase (***MTAP***) genes located on 9p and a tumor suppressor gene closely linked to them is assocd. with acute lymphoblastic leukemia and with gliomas. Alterations were obsd. in DNA sequences on 9p which include the IFN genes at a significant frequency in all typess of human lung cancers (20 of 56 or 36%). The genetic alterations obsd. include homozygous or hemizygous deletions of the IFN genes as well as rearrangement of contiguous DNA sequences. In addn. to these genomic alterations, 10 of 22 (45%) cell lines examd. lacked ***MTAP*** enzyme activity. Overall, 24 of 56 (43%) lung cancer cell lines examd. had hemizygous or homozygous loss of DNA sequences which include the IFN or ***MTAP*** genes. Apparently, the putative tumor suppressor gene at this locus contributes to the malignant process in lung cancers, as well as other types of human cancer.

L10 ANSWER 27 OF 44 CAPLUS COPYRIGHT 1997 ACS DUPLICATE 16
AN 1994:184151 CAPLUS
DN 120:184151
TI The use of methylthioadenosine phosphorylase activity to select for human chromosome 9 in interspecies and intraspecies hybrid cells
AU Porterfield, Bruce W.; Pomykala, Helen; Maltepe, Emin; Bohlander, Stefan K.; Rowley, Janet D.; Diaz, Manuel O.
CS Pritzker Sch. Med., Univ. Chicago, Chicago, IL, 60637, USA
SO Somatic Cell Mol. Genet. (1993), 19(5), 469-77
CODEN: SCMGDN; ISSN: 0740-7750
DT Journal
LA English
AB Methylthioadenosine phosphorylase (***MTAP***) is an enzyme that functions in a salvage pathway for adenine synthesis. The locus that encodes ***MTAP*** activity has been mapped to human chromosome 9 (9q12 9pter) by anal. of mouse .times. human somatic cell hybrids. Cells that have ***MTAP*** activity will stop proliferating, and eventually die in the presence of azaserine, an inhibitor of de novo purine synthesis, but can be rescued by the addn. of methylthioadenosine (MTA) to the culture medium. Some mouse and human tumor cells lack ***MTAP*** activity and can not grow in the presence of azaserine and MTA. The authors fused ***MTAP*** competent human fibroblast cells to ***MTAP*** deficient mouse L-cells and selected for somatic cell hybrids, contg. ***MTAP*** activity, in medium contg. azaserine and MTA.

In a sep. expt., a CHO cell .times. human fibroblast somatic cell hybrid, contg. a normal copy of human chromosome 9, was used to prep. microcells, which were fused to an ***MTAP*** -deficient human leukemic cell line, CCRF-CEM. Somatic cell and microcell hybrids were shown to retain human chromosome 9 by fluorescence in situ hybridization using probes that hybridize to the interferon-alpha and -beta 1 genes on human chromosome 9 (9p21), and the centromere of human chromosome 9. This is the first report of complementation for ***MTAP*** activity being used to select for somatic cell hybrids and microcell hybrids that retain a human chromosome 9.

L10 ANSWER 28 OF 44 CAPLUS COPYRIGHT 1997 ACS DUPLICATE 17
AN 1992:405230 CAPLUS
DN 117:5230
TI Molecular analysis of deletions of the short arm of chromosome 9 in human gliomas
AU Olopade, Olufunmilayo I.; Jenkins, Robert B.; Ransom, David T.; Malik, Kathleen; Pomykala, Helen; Nobori, Tsutomu; Cowan, Janet M.; Rowley, Janet D.; Diaz, Manuel O.
CS Dep. Med., Univ. Chicago, Chicago, IL, 60637, USA
SO Cancer Res. (1992), 52(9), 2523-9
CODEN: CNREA8; ISSN: 0008-5472
DT Journal
LA English
AB Previous studies have suggested that structural abnormalities involving the short arm of chromosome 9 are frequently assocd. with gliomas. The .alpha.-, .beta.-, and .omega.-interferon (IFNA, IFNB1, and IFNW, resp.) and the methylthioadenosine phosphorylase (***MTAP***) genes have been mapped to the short arm of chromosome 9, band p22. Homozygous deletions of these genes have been reported in many leukemia- and glioma-derived cell lines. The authors present a detailed anal. of partial and complete homozygous or hemizygous deletions of DNA sequences on 9p in human cell lines and primary tumor samples of glioma patients. Ten of 15 (67%) glioma-derived cell lines had hemizygous or homozygous deletion of IFN genes or rearrangement of sequences around these genes, while 13 of 35 (37%) primary glioma tumor samples had hemizygous (8 tumors) or homozygous (5 tumors) deletion of the IFN genes. The shortest region of overlap of these deletions maps in the interval between the centromeric end of the IFN gene cluster and the ***MTAP*** gene. In the cell lines and primary tumors examd., these gross genomic alterations were seen only in assocn. with high grade or recurrent gliomas. Apparently, loss of DNA sequences on 9p, particularly the IFN genes, occurs at a significant frequency in gliomas, and may represent an important step in the progression of these tumors. These results are consistent with a model of tumorigenesis in which the development or progression of cancer involves the loss or inactivation of a gene or several genes that normally act to suppress tumorigenesis. One such gene may be located on 9p; this gene may be closely linked to the IFN genes. Nevertheless, loss of the IFN genes, when it occurs, may play an addnl. role in the progression of these tumors.

L10 ANSWER 30 OF 44 CAPLUS COPYRIGHT 1997 ACS DUPLICATE 18
AN 1993:117855 CAPLUS
DN 118:117855
TI Mapping of the shortest region of overlap of deletions of the short arm of chromosome 9 associated with human neoplasia
AU Olopade, Olufunmilayo I.; Bohlander, Stefan K.; Pomykala, Helen; Maltepe, Emin; Van Melle, Elizabeth; Le Beau, Michelle M.; Diaz, Manuel O.
CS Dep. Med., Univ. Chicago, Chicago, IL, 60637, USA
SO Genomics (1992), 14(2), 437-43
CODEN: GNMCEP; ISSN: 0888-7543
DT Journal
LA English
AB Deletions of the short arm of chromosome 9 with a min. region of overlap at band 9p22 are frequently obsd. in acute lymphoblastic leukemia and in gliomas. They also occur at a lower frequency in lymphomas, melanomas, lung cancers, and other solid tumors. These deletions often include the entire interferon (IFN) gene cluster, which comprises about 26 interferon-.alpha. (IFNA),-.omega. (IFNW), and -.beta.-1 (IFNB1) interferon genes, as well as the gene for the enzyme methylthioadenosine phosphorylase (***MTAP***). By comparing microscopic deletions with the genes lost at the mol. level, the authors have detd. the order of these genes on 9p to be telomere-IFNB1-IFNA/IFNW cluster- ***MTAP*** -centromere. In a few cell lines and in primary leukemia cells, the authors have obsd. deletions that have breakpoints within the IFN gene cluster and result in partial loss of the IFN genes. These partial deletions allowed detn. of the order of some genes or groups of genes within the IFNA/IFNW gene cluster. These results map the shortest region of overlap of these deletions in the various tumors to the region between the centromeric end of the IFNA/IFNW gene cluster and the ***MTAP*** gene locus.

L10 ANSWER 31 OF 44 MEDLINE DUPLICATE 19
AN 93079486 MEDLINE
TI [Chromosome abnormalities and adenine metabolism in human glial tumors].
Anomalies chromosomiques et metabolisme de l'adenine dans les tumeurs gliales humaines.
AU Bardot V; Dutrillaux A M; Luccioni C; Poisson M; Delattre J Y; Vega F; Dutrillaux B
CS CEA, DSV/DPTE/LCG, Fontenay-aux-Roses..
SO REVUE NEUROLOGIQUE, (1992) 148 (6-7) 408-16. Ref: 26
Journal code: SU9. ISSN: 0035-3787.
CY France
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA French
FS Priority Journals
EM 9303
AB Most chromosome aberrations in gliomas are numerical, resulting in either gains or deficiencies of whole chromosomes. In tumors of low malignancy, the karyotype is frequently normal or exhibits a loss of sex chromosome and a gain of chromosome 7. These two anomalies may not be directly related to malignancy. In the highly malignant cases, the two most frequent aberrations are the gain of chromosome

7 and the loss of chromosome 10, other anomalies such as losses or deletions of chromosomes, 9, 22, 6, 13 and 14 being detected at various frequencies. Several of these chromosomes carry important genes of adenine metabolism: AK1 and AK3 (adenylate kinase) and ***MTAP*** (methylthioadenosine phosphorylase) for chromosome 9; ADK (adenosine kinase) and mitochondrial ATPase for chromosome 10; ADSL (adenylosuccinate lyase) for chromosome 22, NP (nucleoside phosphorylase) for chromosome 14. We performed the corresponding assays of enzyme activity on both fresh tumors and tumors grafted on nude mice, which showed that these enzymes had a relatively low activity although the tumors were proliferating. However, chromosome losses do not seem to directly cause the metabolic alterations by gene dosage effect. Interestingly, chromosome 10, frequently deficient, also carries genes of importance for glycolysis (hexokinase) and glutamate metabolism (glutamate dehydrogenase and glutamate oxaloacetate transaminase). The deficiency for these genes could be taken into account for a better type of chemotherapy by antimetabolics.

L10 ANSWER 39 OF 44 CAPLUS COPYRIGHT 1997 ACS DUPLICATE 25
AN 1988:165165 CAPLUS
DN 108:165165
TI Transfer of purine metabolites between cells through the medium and via cell contacts in cocultures of HGPRT+ and HGPRT- cells
AU Bols, N. C.; Mosser, D. D.; Boliska, S. A.
CS Dep. Biol., Univ. Waterloo, Waterloo, ON, N2L 3G1, Can.
SO Exp. Cell Res. (1987), 173(1), 206-17
CODEN: ECREAL; ISSN: 0014-4827
DT Journal
LA English
AB Cells with and without hypoxanthine-guanine phosphoribosyltransferase (HGPRT+ and HGPRT-, resp.) activity were used to examine the transfer of purine metabolites through the medium and via cell contacts. HGPRT- Chinese hamster and human fibroblasts were able to incorporate 3H-labeled purine metabolite(s) from medium in which mouse HGPRT+ B82 cells had been grown in 24 h with [3H]hypoxanthine, but HGPRT- mouse A9 fibroblasts that were also deficient in adenine phosphoribosyltransferase (APRT) and methylthioadenosine phosphorylase (***MTAP***) were unable to incorporate these metabolites. Apparently, in recipient cells incorporation is due to [3H]methylthioadenosine, which has been shown previously to be the major 3H-labeled purine metabolite to accumulate in B82 medium, being cleaved by ***MTAP*** to [3H]adenine, which is phosphoribosylated by APRT to [3H]AMP. Incorporation by recipient cells of metabolites from the medium is referred to as contact-independent metabolite transfer (CIMT). In autoradiograms of B82/A9 cocultures that were labeled with [3H]hypoxanthine, grains were found over A9 that were not in contact with B82, although A9 did not act as recipients of CIMT. This is termed proximity-dependent metabolite transfer (PDMT). Both CIMT and PDMT interfered with the assessment of nucleotide exchange between HGPRT+ and HGPRT- cells though cell contacts, which is referred to as contact-dependent metabolite transfer (CDMT). These problems were unique to HGPRT+ mouse L cells. However, HGPRT- mouse L cells, A9, could be used as potential recipients. A9 were pos. recipients of CDMT with only 1 of 5 cell lines tested, which suggests that these cells were selective communicators. CDMT could not be studied with [3H]guanine because the nuclei of HGPRT- cells became labeled.

L10 ANSWER 41 OF 44 CAPLUS COPYRIGHT 1997 ACS DUPLICATE 26
AN 1987:153766 CAPLUS
DN 106:153766
TI Synthesis of purines in human lymphoblast cells deficient in methylthioadenosine phosphorylase activity
AU Gordon, Ross B.; Blackwell, Kay; Emmerson, Bryan T.
CS Princess Alexandra Hosp., Univ. Queensland, Brisbane, 4102, Australia
SO Biochim. Biophys. Acta (1987), 927(1), 1-7
CODEN: BBACAQ; ISSN: 0006-3002
DT Journal
LA English
AB Two human lymphoblastic cell lines deficient in methylthioadenosine phosphorylase (***MTAP***) activity had increased rates of de novo purine synthesis. These ***MTAP*** - cell lines were K532, an undifferentiated leukemic line, and CCRF-CEM, a leukemic line of T-cell origin. Another T-cell line, CCRF-HSB-2 was deficient in activity. However, this line did not demonstrate elevated rates of purine synthesis. Purine metab. in the above cell cultures was compared with ***MTAP*** + human B-cell lines and 2 human T-cell lines (MOLT-3 and MOLT-4). In all the ***MTAP*** + cell lines, the rate of de novo purine synthesis was inhibited by the presence of methylthioadenosine in the assay medium (10 .mu.M concn. produced >90% inhibition). However, purine synthesis in the ***MTAP*** - cell was resistant to inhibition by methylthioadenosine. Adenine in the assay medium inhibited de novo purine synthesis in ***MTAP*** + and ***MTAP*** - cells to a similar degree. This inhibition was dose dependent and was elicited by concns. similar to those of methylthioadenosine. Growth of the cell lines in culture was not affected by either methylthioadenosine or adenine at the concns. which produced inhibition of purine synthesis. Evidently, purine synthesis in ***MTAP*** + cells is inhibited by adenine formed from the phosphorolytic cleavage of methylthioadenosine by methylthioadenosine phosphorylase.